

WHAT IS CLAIMED IS:

1. A method of qualifying ovarian cancer status in a subject comprising:

(a) measuring at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of ApoA1, modified ApoA1, transthyretin $\Delta N10$, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3, and combinations thereof, and

(b) correlating the measurement with ovarian cancer status.

2. The method of claim 1 further comprising:

(c) managing subject treatment based on the status.

3. The method of claim 2, wherein managing subject treatment is selected from ordering more tests, performing surgery, and taking no further action.

4. The method of claim 2 further comprising:

(d) measuring the at least one biomarker after subject management.

5. The method of claim 1 wherein the ovarian cancer status is selected from the group consisting of the subject's risk of cancer, the presence or absence of disease, the stage of disease and the effectiveness of treatment of disease.

6. The method of claim 5 further comprising measuring at least one known biomarker (Marker 4) in a sample from the subject and correlating measurement of the known biomarker and the measurement of ApoA1, modified ApoA1, transthyretin $\Delta N10$, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, or IAIH4 fragment no. 3 with ovarian cancer status.

7. The method of claim 6, wherein the known biomarker is selected from CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, tumor associated trypsin inhibitor (TATI), CEA, placental alkaline phosphatase (PLAP), Sialyl TN, galactosyltransferase, macrophage colony stimulating factor (M-CSF, CSF-1), lysophosphatidic acid (LPA), 110 kD component of the extracellular domain of the epidermal growth factor receptor (p110EGFR), tissue kallikreins, e.g., kallikrein 6 and kallikrein 10 (NES-1), prostasin, HE4, creatine kinase B (CKB), LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB 70/K, Tissue peptide antigen (TPA), osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

8. The method of claim 1, comprising measuring ApoA1 and transthyretin, wherein the ApoA1 is selected from the group consisting of unmodified ApoA1 and modified ApoA1, wherein the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin.

9. The method of claim 8, wherein the ApoA1 is modified ApoA1, and the transthyretin is cysteinylated transthyretin.

10. The method of claim 1 comprising measuring ApoA1, transthyretin and IAIH4 fragment, wherein the ApoA1 is selected from the group consisting of unmodified ApoA1 and modified ApoA1, wherein the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin, and wherein the IAIH4 fragment is selected from the group consisting of IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

11. The method of claim 1 comprising measuring ApoA1, modified ApoA1, transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

12. The method of any one of claims 8-12 further comprising measuring a known biomarker in a sample from the subject and correlating measurement of the known biomarker and the measurements of ApoA1, transthyretin ΔN10 and IAIH4 fragment with ovarian cancer status.

13. The method of claim 12, wherein the known biomarker is selected from CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, TATI, CEA, PLAP, Sialyl TN, galactosyltransferase, M-CSF, CSF-1, LPA, p110EGFR, tissue kallikreins, prostatin, HE4, CKB, LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB 70/K, TPA, osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

14. The method of any one of claims 8-13 wherein measuring comprises:

- (a) providing a subject sample of blood or a blood derivative;
- (b) fractionating proteins in the sample on an anion exchange resin and collecting fractions that contain ApoA1, transthyretin and IAIH4 fragment; and
- (c) capturing ApoA1, transthyretin and IAIH4 fragment from the fractions on a surface of a substrate comprising capture reagents that bind the protein biomarkers.

15. The method of claim 14 wherein the substrate is a SELDI probe comprising an IMAC copper surface and wherein the protein biomarkers are detected by SELDI.

16. The method of claim 14 wherein the substrate is a SELDI probe comprising biospecific affinity reagents that bind ApoA1, transthyretin and IAIH4 fragment and wherein the protein biomarkers are detected by SELDI.

17. The method of claim 14 wherein the substrate is a microtiter plate comprising biospecific affinity reagents that bind ApoA1, transthyretin and IAIH4 fragment and the protein biomarkers are detected by immunoassay.

18. The method of claim 1, wherein measuring is selected from detecting the presence or absence of the biomarker(s), quantifying the amount of marker(s), and qualifying the type of biomarker.

19. The method of claim 1 wherein at least one biomarker is measured using a biochip array.
20. The method of claim 19 wherein the biochip array is a protein chip array.
21. The method of claim 19 wherein the biochip array is a nucleic acid array.
22. The method of claim 19 wherein at least one biomarker is immobilized on the biochip array.
23. The method of claim 1 wherein the protein biomarkers are measured by SELDI.
24. The method of claim 1 wherein the protein biomarkers are measured by immunoassay.
25. The method of claim 1 wherein the correlating is performed by a software classification algorithm.
26. The method of claim 1 wherein the sample is selected from blood, serum and plasma.
27. A method comprising:
 - (a) measuring a plurality of biomarkers in a sample from the subject, wherein the biomarkers are selected from the group consisting of ApoA1, modified ApoA1, transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.
28. The method of claim 27, wherein the plurality includes ApoA1 and transthyretin, wherein the ApoA1 is selected from the group consisting of unmodified ApoA1 and modified ApoA1, and wherein the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin,

sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin.

29. The method of claim 27 wherein the plurality includes ApoA1, transthyretin, and IAIH4 fragment, wherein the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin, and wherein the IAIH4 fragment is selected from the group consisting of IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

30. The method of any one of claims 27-29 further comprising measuring at least one known biomarker.

31. The method of claim 30, wherein the known biomarker is selected from CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, TATI, CEA, PLAP, Sialyl TN, galactosyltransferase, M-CSF, CSF-1, LPA, p110EGFR, tissue kallikreins, prostasin, HE4, CKB, LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB 70/K, TPA, osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

32. The method of anyone one of claims 27-31 wherein the protein biomarkers are detected by SELDI or immunoassay.

33. The method of any one of claims 27-32 wherein the sample is selected from blood, serum and plasma.

34. A method comprising:
measuring at least one biomarker in a sample from a subject, wherein the biomarker is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3, and combinations thereof.

35. The method of claim 34 further comprising measuring ApoA1.

36. The method of claim 35, wherein the ApoA1 is modified ApoA1.

37. The method of any one of claims 34-36 further comprising measuring at least one known biomarker.

38. The method of claim 37, wherein the known biomarker is selected from CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, TATI, CEA, PLAP, Sialyl TN, galactosyltransferase, M-CSF, CSF-1, LPA, p110EGFR, tissue kallikreins, prostasin, HE4, CKB, LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB 70/K, TPA, osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

39. The method of any one of claims 34-38 wherein the protein biomarkers are detected by SELDI or immunoassay.

40. The method of any one of claims 34-39 wherein the sample is selected from blood, serum and plasma.

41. A kit comprising:

(a) a capture reagent that binds a biomarker selected from ApoA1, modified ApoA1, transthyretin ΔN10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3, and combinations thereof; and

(b) a container comprising at least one of the biomarkers.

42. The kit of claim 41 wherein the capture reagent binds a plurality of the biomarkers.

43. The kit of any one of claims 41-42 wherein the capture reagent is a SELDI probe.

44. The kit of any one of claims 41-43 further comprising a capture reagent that binds CA125.

45. The kit of any one of claims 41-44 further comprising a second capture reagent that binds one of the biomarkers that the first capture reagent does not bind.

46. A kit comprising:

- (a) a first capture reagent that binds at least one biomarker selected from ApoA1, modified ApoA1, transthyretin Δ N10, native transthyretin, cystenylated transthyretin, gluationylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3, and
- (b) a second capture reagent that binds at least one of the biomarkers that is not bound by the first capture reagent.

47. The kit of claim 46 wherein the at least one capture reagent is an antibody.

48. The kit of any one of claims 46-47 further comprising an MS probe to which at least one capture reagent is attached or is attachable.

49. The kit of any one of claims 46-48 wherein the capture reagent is an immobilized metal chelate.

50. The kit of any one of claims 46-49 further comprising a wash solution that selectively allows retention of the bound biomarker to the capture reagent as compared with other biomarkers after washing.

51. A kit comprising:

- (a) a first capture reagent that binds at least one biomarker selected from ApoA1, modified ApoA1, transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3, and
- (b) instructions for using the capture reagent to detect the biomarker.

52. The kit of claim 51 wherein the capture reagent is an antibody.

53. The kit of any one of claims 51-52 further comprising an MS probe to which the capture reagent is attached or is attachable.

54. The kit of any one of claims 51-53 wherein the capture reagent is an immobilized metal chelate.

55. The kit of any one of claims 51-55 further comprising a wash solution that selectively allows retention of the bound biomarker to the capture reagent as compared with other biomarkers after washing.

56. The kit of any one of claims 51-55 further comprising written instructions for use of the kit for detection of cancer.

57. The kit of claim 56 wherein the instructions provide for contacting a test sample with the capture agent and detecting one or more biomarkers retained by the capture agent.

58. A purified peptide selected from the group consisting of SEQ ID NO:1 (IAIH4 fragment no. 1), SEQ ID NO:2 (IAIH4 fragment no. 2), and SEQ ID NO:3 (IAIH4 fragment no. 3).

59. The peptide of claim 58 further comprising a detectable label.

60. An article manufacture comprising:

(a) at least one capture reagent that binds to at least two biomarkers selected from ApoA1, modified ApoA1, transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

61. The article of manufacture of claim 60, wherein the biomarkers are ApoA1 and transthyretin, wherein the ApoA1 is selected from the group consisting of unmodified ApoA1 and modified ApoA1, and wherein the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin.

62. The article of manufacture of claim 60 wherein the biomarkers are ApoA1, transthyretin, and IAIH4 fragment, wherein the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin, and wherein the IAIH4 fragment is selected from the

group consisting of IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

63. The article of manufacture of any one of claims 60-62 further comprising a capture reagent that binds to at least one known biomarker.

64. The article of manufacture of claim 63, wherein the known biomarker is selected from CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, TATI, CEA, PLAP, Sialyl TN, galactosyltransferase, M-CSF, CSF-1, LPA, p110EGFR, tissue kallikreins, prostatin, HE4, CKB, LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB 70/K, TPA, osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

65. A system comprising:

(a) a plurality of capture reagents each of which has bound to it a different biomarker selected from ApoA1, modified ApoA1, transthyretin ΔN10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, IAIH4 fragment no. 3, and CA 125

66. A screening test comprising:

(a) contacting a kallikrein with a kallikrein substrate and with a test agent and
(b) determining whether the test agent modulates the activity of the kallikrein.

67. The test of claim 66 wherein the substrate is inter-alpha-trypsin inhibitor heavy chain H4 precursor.

68. The test of claim 66 wherein the kallikrein cleaves the substrate into IAIH4 fragment no. 1, IAIH4 fragment no. 2, or IAIH4 fragment no. 3.

69. The test of claim 66, wherein the determining step further comprises measuring biomarker IAIH4 fragment no. 1, IAIH4 fragment no. 2, or IAIH4 fragment no. 3.,

70. The test of claim 69, wherein the protein biomarkers are measured by SELDI.

71. The test of claim 69, wherein the protein biomarkers are measured by immunoassay.

72. A method of qualifying ovarian cancer status in a subject comprising:

(a) measuring at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of Markers I through XLVIII and combinations thereof, and

(b) correlating the measurement with ovarian cancer status.

73. The method of claim 72 further comprising:

(c) managing subject treatment based on the status.

74. The method of claim 73, wherein managing subject treatment is selected from ordering more tests, performing surgery, and taking no further action.

75. The method of claim 73 further comprising:

(d) measuring the at least one biomarker after subject management.

76. The method of claim 72 wherein the ovarian cancer status is selected from the group consisting of the subject's risk of cancer, the presence or absence of disease, the stage of disease and the effectiveness of treatment of disease.

77. The method of any one of claims 72-77 further comprising measuring at least one known biomarker in a sample from the subject and correlating measurement of at least one known biomarker and the measurement of least marker of the group consisting of Markers I through XLVIII with ovarian cancer status.

78. The method of claim 77, wherein the known biomarker is selected from ApoA1, transthyretin, IAIH4 fragment, CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, TATI, CEA, PLAP, Sialyl TN, galactosyltransferase, M-CSF, CSF-I, LPA, p110EGFR, tissue kallikreins, prostasin, HE4, CKB, LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB 70/K, TPA, osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

79. The method of any one of claims 72-78 wherein measuring comprises:

(a) providing a subject sample of blood or a blood derivative;

(b) fractionating proteins in the sample on an anion exchange resin and collecting fractions that contain any of the biomarkers selected from the group consisting of Markers I through XLVIII; and

(c) capturing the biomarker from the fractions on a surface of a substrate comprising capture reagents that bind the protein biomarkers.

80. The method of claim 79 wherein the substrate is a SELDI probe comprising an IMAC copper surface and wherein the protein biomarkers are detected by SELDI.

81. The method of claim 79 wherein the substrate is a SELDI probe comprising biospecific affinity reagents that bind any of the biomarkers selected from the group consisting of Markers I through XLVIII and wherein the protein biomarkers are detected by SELDI.

82. The method of any one of claims 72-81 further comprising measuring at least one biomarker selected from ApoA1, modified ApoA1, transthyretin $\Delta N10$, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3, in a sample from the subject and correlating measurement of the biomarker and the measurement of least marker of the group consisting of Markers I through XLVIII with ovarian cancer status.

83. A software product comprising:

a. code that accesses data attributed to a sample, the data comprising measurement of at least one biomarker in the sample, the biomarker selected from the group consisting of ApoA1, modified ApoA1, transthyretin $\Delta N10$, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3; and

b. code that executes a classification algorithm that classifies the ovarian cancer status of the sample as a function of the measurement.

84. The software product of claim 83, wherein the classification algorithm classifies the ovarian cancer status of the sample as a function of the measurement of a biomarker selected from the group consisting of: ApoA1, modified ApoA1, transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

85. The software product of claim 83, wherein the classification algorithm classifies the ovarian cancer status of the sample as a function of the measurement of each of the biomarkers: ApoA1 and transthyretin, wherein the ApoA1 is selected from the group consisting of unmodified ApoA1, and the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin.

86. The software product of claim 83, wherein the classification algorithm classifies the ovarian cancer status of the sample as a function of the measurement of each of the biomarkers: ApoA1, transthyretin, and IAIH4 fragment, wherein the ApoA1 is selected from the group consisting of unmodified ApoA1, the transthyretin is selected from the group consisting of transthyretin Δ N10, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin, and wherein the IAIH4 fragment is selected from the group consisting of IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

87. The software product of any one of claims 83-86, wherein the classification algorithm classifies the ovarian cancer status of the sample further as a function of the measurement of a known biomarker.

88. The software product of claim 87, wherein the known biomarker is selected from the group consisting of: ApoA1, transthyretin Δ N10, IAIH4 fragment, CA125, CA125 II, CA15-3, CA19-9, CA72-4, CA 195, TATI, CEA, PLAP, Sialyl TN, galactosyltransferase, M-CSF, CSF-1, LPA, p110EGFR, tissue kallikreins, prostasin, HE4, CKB, LASA, HER-2/neu, urinary gonadotropin peptide, Dianon NB

70/K, TPA, osteopontin and haptoglobin, and protein variants (e.g., cleavage forms, isoforms) of the markers.

89. A method comprising detecting a biomarker selected from the group consisting of ApoA1, modified ApoA1, transthyretin $\Delta N10$, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3 by mass spectrometry or immunoassay.

90. A method comprising communicating to a subject a diagnosis relating to ovarian cancer status determined from the correlation of biomarkers in a sample from the subject, wherein said biomarkers are selected from the group consisting of ApoA1, modified ApoA1, transthyretin $\Delta N10$, native transthyretin, cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, glutathionylated transthyretin, IAIH4 fragment no. 1, IAIH4 fragment no. 2, and IAIH4 fragment no. 3.

91. The method of claim 90, wherein the diagnosis is communicated to the subject via a computer-generated medium.

92. A method for identifying a compound that interacts with IAIH4, wherein said method comprises:

- a) contacting IAIH4 with a test compound; and
- b) determining whether the test compound interacts with IAIH4.

93. A method for identifying a compound that interacts with IAIH4, wherein said method comprises:

- a) contacting IAIH4 with a test compound; and
- b) determining whether the test compound interacts with IAIH4.

94. A method for modulating the concentration of IAIH4 in a cell, wherein said method comprises:

a) contacting said cell with a protease inhibitor, wherein said protease inhibitor prevents cleavage of LAIH4.

95. A method of treating a condition in a subject, wherein said method comprises administering to a subject a therapeutically effective amount of a compound which modulates the expression or activity of a protease which cleaves LAIH4.

96. A method comprising:

a) assigning a probability that a data set is classified into each of at least two groups; and

b) determining an index of the data set, wherein the index is a function of each of the probabilities.

97. The method of claim 96 wherein the data set comprises at least one or more measurements selected from the group consisting of: a plurality of biomarkers, clinical history, genotype, and laboratory testing.

98. The method of claim 96 wherein the function is a sum of functions of each of the probabilities.

99. The method of claim 96, wherein the probabilities are selected from the group consisting of: relative risk, odds ratio, and hazards ratio.